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GUEST EDITORIAL

Estrogen Replacement Therapy for the Breast Cancer Survivor: A Reappraisal

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INTRODUCTION

One of the most emotionally charged subjects in the field of oncology is the issue of whether a breast cancer patient who is disease free can be permitted to enjoy the benefits of hormone replacement therapy (HRT). In this report, HRT is used as a general term implying the use of estrogen replacement therapy with or without concomitant progestin therapy. Simply stated, the issue is whether physiological dosages of HRT will produce a negative impact on the disease-free survival of this group of women; this concept has been termed the ''fuel on the fire'' theory.

Given the millions of American women who have survived this disease, which has an annual incidence in the United States of 180–185,000 cases and an overall disease-free survival at 5 years in excess of 70%, there is ample reason for study of this controversial question. In addition, the recent broadening of indications for adjuvant chemotherapy has created greatly increased numbers of premenopausal patients (ages 25–45) who are rendered prematurely menopausal by the effect of the cytotoxic drugs on their ovarian function.

In the last two decades, two demographic trends have heightened awareness concerning menopause and its health consequences. First and foremost, women are living longer. Life expectancy for U.S. women in 1900 was age 45, and now it is close to 80. Most women are spending fully 40% of their life after menopause. Second, more women than ever will enter the menopausal years in the next decade as millions of babyboomers, those born after World War II, enter their fifties. The proportion of all U.S. women older than 45 years of age will grow from 34% in 1995 to 43% in the year 2020.

The benefits of HRT are well documented in the literature. Relief of menopausal symptoms such as ''hot flashes,'' vaginal atrophy, vaginal dryness with dyspareunia, and insomnia are those most frequently listed since they relate to quality-of-life issues. In this same category, one should include the positive effects of estrogen on urinary tract epithelium resulting in relief of symptoms of urgency, frequency, nocturia, and stress incontinence. Other benefits include relief of anxiety, irritability, and depression. All of these changes can have a great impact on the quality of life of many women and often become the most immediate justification for considering HRT in any patient. In point of fact, there are additional important health issues of a more long-term nature, which also deserves serious consideration.

HRT has been shown to have a profound impact on conditions such as osteoporosis [1,2], cardiovascular disease, and colon cancer, and recent evidence also suggests cognitive function. The PEPI Trial [3] evaluated 875 postmenopausal women in a multicenter, randomized, placebo-controlled study of estrogen replacement therapy. The women taking hormone therapy had increased bone mineral density compared to nonusers regardless of age, years from menopause, body mass, prior estrogen use, baseline bone mineral density, or smoking and physical status. Other studies have demonstrated a reduced incidence of most types of bone fractures in women taking HRT. This includes hip fractures, which carry up to a 20% mortality for elderly women during the 6 months following the event. The effects of HRT on cardiovascular disease are well documented, consistent, and statistically significant. Total deaths from cardiovascular disease in U.S. women exceeds deaths from breast cancer by a factor of 10. The U.S. Food and Drug Administration (FDA) reviewed data on the cardioprotective effect of estrogen on two occasions in the 1990s. Both reviews agreed that HRT seems to confer substantial protection against cardiovascular disease. Interestingly, the FDA has not added these findings as an indication for estrogen therapy. Stampfer and Colditz [4] analyzed the results of 29 epidemiologic studies that provided information on HRT and coronary artery disease,

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and they found that estrogen replacement therapy (ERT) carries a 50% reduction in the risk of cardiovascular disease. ERT probably exerts its cardioprotective effect via several mechanisms, including the induction of a favorable lipid profile, inhibition of the deposition of cholesterol in the arterial wall, decreased fibrinogen levels, and improved vasomotor tone and blood flow [5]. The PEPI Trial overcomes most criticisms of previous reports because of its randomized placebo-controlled profile.

Three published studies suggest that HRT may help protect women against colorectal cancer [6–8]. Significantly reduced risks (RR = 0.5) of colorectal neoplasms have been found in both past users and currently users with the greatest effect seen with long duration of use.

RISK OF BREAST CANCER WITH ESTROGEN THERAPY

All aspects of medical practice require a risk/benefit analysis for any mode of therapy. In the case of HRT for breast cancer survivors, the benefits are well established, but the risks are uncertain [9–14]. What is needed is a prospective randomized trial of HRT vs. placebo that is monitored for at least a 5–10-year interval. It is estimated that in the range of 5,000 patients, it may be necessary for such a trial, making it very expensive and difficult to fund. In the absence of such a study, some information can be extracted from the serendipitous exposure of an occult or subclinical breast cancer to either endogenous or exogenous estrogen, e.g., concomitant or subsequent pregnancy or recent use of either birth control pills or exogenous estrogen. What is the impact of exposing patients with occult disease to these increased levels of estrogen? Is their survival adversely effected?

Approximately 10–20% of breast cancers occur in women ages 15–44, and 0.5–4% are diagnosed either during pregnancy or lactation. On the average, a malignant breast lesion lies occultly in the breast some 5–8 years prior to clinical detection. Thus patients who have been pregnant within 1–2 years of diagnosis certainly have had a lesion exposed to high levels of placental hormones, especially estriol. Do these patients do worse than comparable patients who are not pregnant? The answer is no. When pregnant patients with breast cancer are compared with nonpregnant breast cancer patients of similar age and stage of disease, the pregnant state does not confer a worse prognosis [15,16]. Several investigators have shown that neither spontaneous or therapeutic abortion appears to influence the course of breast cancer in these young patients. Youthful patients tend to survive less well and are more likely to have positive axillary nodes whether they are pregnant or not. However, from the point of diagnosis, the pregnant patient does as well as the comparable nonpregnant patient.

Women of reproductive age may decide to become pregnant following therapy for breast cancer. There are several reports [17–19] in the literature of such women and their survival statistics. Some of these reports suggest that breast cancer patients who subsequently choose to become pregnant appear to survive longer than comparable patients who did not become pregnant, even after eliminating biases for women with poor prognoses who are advised not to conceive and for women who were unlikely to become pregnant because of recurrent disease. In summary, those reports on this subject have found no adverse effect on survival from breast cancer in patients where subsequent pregnancies occur. In summary, pregnancy coincident with breast cancer or subsequent to therapy lends no support to the ''fuel on the fire'' theory.

Given the long natural history of this neoplasm, it is reasonable to assume that a modest number of women subsequently diagnosed with breast cancer used oral contraceptives (OCs) during the promotion and progression of their malignancy in the breast. Most of the data in the literature pertains to the incidence of breast cancer in previous and current users of OCs. However, at least two reports [20,21] single out those patients who used OCs within 1 year of diagnosis, and both reports show no diminished survival in the OC users as compared to nonusers of similar age and stage.

Noncontraceptive estrogens were first marketed in the United States in 1942. Whether and to what degree ERT and HRT affects breast cancer risk is not clear, despite a large number of studies. Some studies show an increased risk of breast cancer, some show an elevated risk only among certain subgroups, and many studies show no increased risk. Some authors believe that the addition of progestin confers a protective effect; others argue the opposite. Estrogens are likely to have some influence on breast cancer, since several reproductive events correlate with increased breast cancer risk, e.g., early age at menarche, late age of menopause, late age of first birth, and nulliparity. However, reproductive factors alone do not adequately explain the etiology of breast cancer. Other factors that influence risk are genetics, obesity, age, diet, alcohol consumption, exposure to radiation, and many as yet unknown elements.

Two reports, published in July 1995, are characteristic of the controversy surrounding breast cancer risk in women taking HRT. The first report [22] was from the Nurses Health Study, and it updated data that indicated a modest rise of risk for current users (not past users) as compared to women who had never used estrogen (RR = 1.3 95% Cl, 1.1–1.5). Those current users of estrogen plus progestin had a similar risk (RR = 1.4; 95% Cl, 1.2–1.7). With greater than 10 years of use, the risk rose to RR = 1.5 (95% Cl; 1.2–1.8). The second report [12] found no increased risk for estrogen users (RR = 0.9; 95% Cl 0.7–1.3). This was a population-based case control study using data from the Seattle-Pugent Sound Sur-

veillance, Epidemiology, and End Results cancer registry on 537 women with primary breast cancer. Neither long term use (>20 years) or combined estrogen-progestin therapy elevated the risk of breast cancer. This disagreement and that seen in over 50 studies in the literature undoubtedly implies that if there is an adverse influence of HRT on breast cancer risk, it must be small and not easily reproduced. Four meta-analyses suggest that with greater than 10 years of use, the added risk can go up about 30%. Although the popular use of the meta-analyses helps to solve the problem that individual studies do not have the statistical power to overcome biases, the technique does not overcome the variability in individual studies. Indeed, many epidemiologists insist that the use of meta-analyses be reserved for randomized trials only, and no randomized trials were included in the four meta-analyses described above.

The incidence data quoted above is only indirectly relevant to the subject of the impact of HRT on the breast cancer patient. More to the point, a report by Bergkvist in 1989 [23] compared 261 women who developed breast cancer in a population-based cohort of estrogen-treated women with 6,617 breast cancer patients who had no recorded estrogen usage. The relative survival rate was significantly higher, by ~10 percentage points at 8 years, in the patients who had received estrogen therapy, corresponding to an ~40% reduction in excess mortality. The time from the use of estrogen to diagnosis as well as the total duration of use were unrelated to survival. When the effect of current use was taken into account in a multivaried analysis, no impact on survival was seen. A similar study by Strickland [24] came to the same conclusion with regard to current use of HRT in women diagnosed with breast cancer. It seems reasonable to assume that women diagnosed with breast cancer while taking HRT have had a lesion in the breast that has had years of exposure to the hormone therapy (fuel for the fire). Yet these women do not demonstrate an adverse effect on their survival from this exposure.

In 1989, Dupont and Page [25] reported their reevaluation of 10,366 consecutive benign breast biopsies performed at their institution over an 18-year period. Followup was possible on 3,303 of the women for a median duration of 17 years. The authors were able to define a premalignant histologic state called ''proliferative disease,'' which carried an increased risk ratio (RR) for breast cancer of 1.9. When the proliferative disease state was associated with atypia, the RR was 4.5. Exogenous estrogen use actually lowered the breast cancer risk (RR = 0.92 vs. 1.9) in all women (0.92 vs. 1.9), including patients with atypical hyperplasia (3.0 vs 4.5). This report suggested that even high-risk women with biopsy-proven, atypical hyperplasia were not at increased risk of developing breast cancer if they choose to use hormone replacement therapy.

What about tamoxifen therapy [26]? This so-called antiestrogen is an active agent in breast cancer therapy. Doesn't that fact suggest that estrogen therapy would be harmful? Can HRT be given to patients on tamoxifen therapy? Tamoxifen is not an ''antiestrogen,'' but it is really a weak estrogen and has many properties attributable to estrogen. Tamoxifen reduces blood cholesterol by an average of 12% and low-density lipoprotein cholesterol by 20% [27,28]. Reports are also available showing a reduction of cardiovascular events in tamoxifen-treated women, who are at a slightly increased risk of developing endometrial cancer [29,30]. Histological study of the endometrium of patients on tamoxifen reveals a marked tendency to proliferation and polyp formation. The ability of 20 mg of tamoxifen given orally to suppress FSH (follicle stimulating hormone) levels in premenopausal women is almost as effective as 2 mg of estradiol (26% vs. 36%). The author has prescribed HRT for breast cancer survivors on tamoxifen and observed no diminished effectiveness of the estrogen therapy in terms of relief of symptoms or tissue restoration. Tamoxifen has many actions at a cellular level, especially on growth factors, that can adequately explain its therapeutic effect on breast cancer independent of its affinity for the estrogen receptor. At low drug concentrations, tamoxifen exerts cytostatic effects by increasing the G_1-phase duration of the cell cycle and shifting cells from the rapidly cycling pool to the slowly cycling pool. Higher concentrations are cytotoxic, producing a specific G_1 blockade, which cannot be reversed by estradiol. The anti-proliferative effects of tamoxifen also can be mediated throughout its effect on multiple polypeptide growth factors. It inhibits the secretion by breast cancer cells of transforming growth factor-alpha as well as epidermal growth factors and stimulates production of transforming growth factor-beta. Both transforming growth factor-alpha and epidermal growth factor have been demonstrated to promote breast cancer cell growth. Transforming growth factor beta inhibits the growth of various epithelial cell lines, including ER-negative breast cancer cells. Additional antiproliferative effects of tamoxifen may be related to its inhibition of protein kinase C, its binding of calmodulin, and its ability to decrease insulin—like growth factor I.

The author is currently following a group of 120 breast cancer survivors who have chosen HRT use for themselves. All of these patients were thoroughly counseled regarding the theoretical hazards and the well-substantiated benefits. Patients were not excluded because of positive node status or positive estrogen receptor status. Every patient understood that HRT would not prevent a recurrence of their malignant disease. The patients also understood that this author is convinced that, currently, there is no solid clinical evidence that such therapy will adversely affect the outcome of their malignant disease. To date, there have been several recurrences

of breast cancer (10%) among this group of 120 patients. A preliminary analyses of the first 77 patients was reported in a letter to the editor in Lancet, 1993 [31]. What follows is a more detailed analysis of that group of 77 patients who have had the longest followup.

The median age at diagnosis in the group was 50 years (range 26–88). A large majority of the patients were between 40 and 60 years of age. Interestingly, seven of the patients previously had a second primary gynecological cancer, (4 endometrial, 2 ovary, and 1 cervix). Of the patients, 56% were Stage I, and 22% were Stage II; 18% had positive lymph nodes at the time of initial therapy, and 62% had a histological diagnosis of ductal carcinoma. Receptor status was known on only 40 of the patients. Receptor status was not a consideration in prescribing HRT. In fact, out of the 40 patients whose receptor status was known, 28 patients (70%) were estrogen receptive positive. Nearly 50% of the patients were individuals who became menopausal during or shortly following adjuvant chemotherapy. An additional 28 patients (36%) had been on postmenopausal HRT at the time of the diagnosis of breast cancer. Interestingly, 25 of the 28 patients, who were users of HRT at the time of diagnosis, had negative nodes. This may represent a clinical bias since patients on HRT may be monitored more carefully.

The median interval between diagnosis and the start of HRT was 24 months, with 37 (48%) of the patients starting within 24 months. All but 13 of the patients received a combination of estrogen plus progestin. Most of the patients received HRT as conjugated estrogen with three of the patients using estradiol patches. Some 30 patients (39%) were on concomitant tamoxifen therapy during some interval of HRT. Tamoxifen was considered a chemotherapeutic agent and was continued as long as desired by the patient and her oncologist. Those patients on HRT and tamoxifen did not differ clinically from patients on HRT alone; hot flushes and vaginal dryness disappeared and the patients appeared optimally estrogenized. The median followup from diagnosis was 59 months, and the median disease-free survival was 53 months.

Seven of the 77 women had breast cancer recurrence after starting HRT (average interval from diagnosis to relapse was 45.3 months). Of these seven patients, five were still taking HRT at the time of recurrence, whereas two had stopped HRT before recurrence was diagnosed. Four of the five patients, who were still on HRT at the time of recurrence, stopped HRT at the time of the diagnosis of recurrence: one was alive with no evidence of disease, two were alive with disease, and one died of disease. The fifth patient continued treatment with HRT despite having relapsed; she was alive with no evidence of disease at the time of the report.

Of the initial 77 patients started on HRT, 72 (92%) had no evidence of disease [32]. Two patients (3%) were alive with disease; three had died, one of complications from chemotherapy (at autopsy she was free of demonstrable disease); and two of progressive disease. Among the 70 patients with no evidence of recurrence, only three had stopped taking HRT. The interval between the onset of HRT and recurrence was carefully examined. Two patients recurred 8 and 10 months after initiation of HRT; the other five patients recurred at 27, 36, 36, 60, and 80 months.

Eden [33] reported a case control study of combined continuous HRT among women with a personal history of breast cancer. His objective was to examine the effect on general mortality and tumor recurrence rate of combined continuous HRT given to symptomatic menopausal women with a personal history of breast cancer. He performed a case-controlled study in a cohort of women with a personal history of breast cancer. The entire database comprised of 901 women with surgically confirmed breast cancer attending one of three teaching hospitals in southeastern Sidney, Australia. Ninety had taken estrogen for relief of severe menopausal symptoms after their diagnosis and treatment of breast cancer. Most were using combined continuous HRT, usually an oral estrogen with a moderate dosage progestin. Controls were matched subjects from the same database who had not taken sex hormones after their diagnosis of cancer. The main outcome measures were all-cause mortality and recurrence of breast cancer (or new contralateral breast cancer). Relative risks were then calculated comparing sex hormone users with matched controls. Among the 90 estrogen users, there were no deaths, and only 7% developed a recurrence, compared to 17% of the nonusers (using two matched controls; RR = 0.40). These results suggest that short-term usage of combined continuous HRT by women with a personal history of breast cancer may be safe and might even reduce the risk of recurrence. They also concluded that a formal prospective double-blind study is needed to confirm their results.

RISK OF BREAST CANCER AND PROGESTIN THERAPY

The addition of a progestational agent to postmenopausal estrogen therapy is now accepted as a standard part of the treatment program. The obvious reason for this approach is the need to prevent the increased risk of endometrial cancer associated with exposure to unopposed estrogen. Even though endometrial cancer is not frequently encountered and survival rates are excellent with early disease, the fear of this cancer is a major force in patient continuance, warranting a combined approach. In addition, clinicians and patients have rapidly turned to the method of a continuous combination of estrogen and progestin in order to overcome uterine bleeding, which is the second major continuance problem.

Two reports have claimed that the addition of a pro-

gestational agent protects against breast cancer. The first, by Gambrell [34], was limited by bias in treatment selection (the breast cancer risk factor profiles were not matched in the treated and untreated groups). The second, the Nachtigall study [35], although it is the only randomized, placebo-control trial, was hampered by small numbers.

One aspect of HRT and breast cancer that has not been widely studied is the effect of HRT on the preclinical malignancy itself. Jones analyzed data from women in relation to their use of HRT leading up to their diagnosis of breast cancer. A questionnaire was sent out to women seeking information on the use of HRT before breast cancer surgery. To qualify as HRT users, HRT had to have been used continuously for 6 months or more up to within 2 weeks of surgery. A total of 460 women in western Australian with breast cancer, who were 40 years of age or older at the time of their breast cancer surgery, were sent these brochures; 87% of the questionnaires were recovered, and 39 HRT users and 258 nonusers were analyzed. Twenty-five HRT users used a combination of estrogen and progesterone and 14 used estrogen only. Twenty-six had used HRT for >2 years and 13 for 2 years or less at the time of breast cancer diagnosis. Biochemical indices of estrogen receptor, cathepsin D, and protein levels, as well as pathological indices of tumor size, tumor differentiation, and lymph node involvement for users and nonusers of HRT, were measured. There were no significant differences in the tumor indices between users and nonusers. The mean level of estrogen receptors appeared to be lower in the estrogen-only users than in the combination HRT users and nonusers. The mean cathepsin D level was significantly higher in estrogen-only users than in the nonusers. The percentage of all HRT users with involved lymph nodes (23%) was significantly lower than the percentage of nonusers (44%). Their conclusion was that estrogen-only HRT may have a detrimental effect on tumor biology. However, the use of a progestin in combination with estrogen may offer some protection. Yet, HRT users had less lymph node involvement with tumor. This may reflect early detection with increased surveillance in women using HRT.

Stanford [12] attempted to determine the risk of breast cancer in relation to the use of combined estrogen progestin therapy in a group of women from western Washington State. The women selected were aged 50–64 years, including 537 patients with primary breast cancer diagnosed between January 1, 1988, and June 30, 1990, who were selected through the Seattle-Puget Sound Surveillance, Epidemiology, and End Results cancer registry. A total of 492 randomly selected control women without a history of breast cancer were also selected. Menopausal hormones of some type had been used by 57.6% of the breast cancer cases and 61%of the comparison women. Women who had ever taken combined HRT represented 21.5% of cases and 21.3% of controls. These women were not at increased risk of breast cancer (relative odds = 0.9). Compared with nonusers of menopausal hormones, those who used estrogen-progestin for 8 or more years had, if anything, a reduced risk of breast cancer (relative odds = 0.4). The authors concluded that the use of estrogen with progestin did not appear to be associated with increased risk of breast cancer in middle-age women. They also concluded that the use of combined HRT was only recently prevalent, and future investigations must assess whether breast cancer incidence truly alters many years after HRT has been initiated in long-term users.

At the present time, the available epidemiologic evidence on the impact of combined estrogen-progestin treatment on the risk of breast cancer is still too limited. Neither a protective nor a detrimental effect has yet to be convincingly demonstrated. The Nurses' Health Study group finds that the addition of a progestin does not change the findings with estrogen alone. Balancing the information available involving all the health issues affected by hormone therapy, a combined estrogen-progestin program in appropriate doses continues to offer significant benefits for postmenopausal women.

CONCLUSIONS

The benefits of HRT both to the quality of life of postmenopausal women and the prevention of serious disease processes have been widely published. There has not been a prospective randomized study of breast cancer survivors to answer the question of risk associated with the use of HRT. Even if one could overcome the emotional objections to such a study, its execution would require handsome funding and large numbers of patients (e.g., at least 5,000). This makes such a trial unlikely and certainly not helpful to the clinician in the near future. In the interim, as practicing clinicians, can we avoid the responsibility of thoroughly informing our patients of the benefits as well as the potential risks of HRT and then allowing them to decide on a course of action? Is it proper to continue a practice of categorically prohibiting all breast cancer survivors from utilizing HRT? I think not.

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